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(54) Title: COMBINATION THERAPY FOR LOWER URINARY TRACT SYMPTOMS

(57) Abstract: This invention relates to combination therapy for the treatment of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) associated with or without BPH. The combination therapy comprises of 1a adrenergic receptor (AR) subtype selective antagonist in combination with muscarinic receptor antagonist and optionally included 5 -reductase inhibitor for relief of LUTS in a subject with or without BPH.

COMBINATION THERAPY FOR LOWER URINARY TRACT SYMPTOMS

Field of the Invention

This invention relates to combination therapy for the treatment of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS), whether or not associated with BPH. The combination therapy comprises the use of α_{1a} adrenergic receptor (AR) subtype selective antagonists in combination with muscarinic receptor antagonists and optionally including 5 α -reductase inhibitors, for relief of LUTS in a subject, with or without BPH.

10 Background of the Invention

Benign prostatic hyperplasia (BPH) also known as benign prostatic hypertrophy is highly prevalent in men beyond the age of 50 and increases in severity and incidence with increasing age. The incidence is 70% in 70 years and becomes nearly universal with advancing age with 90% incidence at the age of 80 years [Berry et al., *J. Urol.* 132: 474-15 479 (1984)].

Symptomatic BPH is thought to be due to bladder outflow obstruction and is usually suggestive of the lower urinary tract symptoms [Speakman, *Eur. Urol. Suppl.* 40, 21, (2001)]. BPH is characterized by nodular enlargement of prostatic tissue and is associated with variety of lower urinary tract symptoms (LUTS). LUTS in men includes, 20 but is not, restricted to a complex of obstructive (voiding) and irritative (storage or filling) symptoms which include increased frequency, nocturia, a poor urinary stream and hesitancy or delay in starting urinary flow. Chronic consequences of BPH can include hypertrophy of bladder smooth muscle, a decompensated bladder and increased incidence 25 of urinary tract infections. Histologically, BPH is characterized by glandular (epithelial) and stromal (fibromuscular) hyperplasia with the latter being the dominant factor in the pathogenesis of clinically significant BPH [Shapiro et al, *J Urol* 147: 1293-1297 (1992)].

Though the exact etiology of origin of these symptoms is not distinctly clear, two components, a static component and a dynamic component, clearly contribute to obstruction. Prostatic enlargement or hyperplasia of prostate gland physically impinges on 30 the free flow of fluids through the male urethra and leads to varying degrees of bladder obstruction. This component has been referred to as the static component [Caine M, *J.*

Urol. 136: 1-4 (1986)]. Increased adrenergic innervation to prostate leads to an increased adrenergic tone of the bladder neck or urethra and is referred to as dynamic component. The irritative symptoms have been closely associated with bladder dysfunction which was believed to be a consequence of bladder outlet obstruction [Anderson K. E., *Brit. J. Urol.* 85 Suppl: 12-18 (2000)].

Standard treatments for BPH involve surgical or pharmacological intervention. Surgical intervention involves removal of the prostate via radical prostatectomy or removing the prostate adenoma via transurethral resection of the prostate. These invasive surgical procedures have limited utility because of the morbidity associated with operative procedures as well as the persistence and recurrence of obstructive and irritative symptoms. Surgical procedures are, therefore, not recommended for patients exhibiting mild to moderate symptoms.

Presently, pharmacological interventions in the treatment of BPH can be distinctly categorized into two main categories: - α_1 AR antagonists and testosterone 5α -reductase inhibitors. Testosterone 5α reductase inhibitors such as finasteride and dutasteride reduce the size of prostate [Wilde et al., *Drugs* 57: 557-581 (1999)], thereby alleviating the static component of bladder outlet obstruction. The lesser efficacy associated with these inhibitors is mechanism-based, in that testosterone 5α -reductase inhibitors decrease the size of prostate by reducing the amount of epithelial tissue without affecting the smooth muscle and the dynamic component of bladder outlet obstruction.

Other pharmacological therapy involves the administration of subtype non-selective α_1 AR antagonists. These agents relax prostatic-urethral smooth muscle by blocking the α_1 mediated effects on endogenous tone hence affecting the dynamic component of bladder outlet obstruction and relieving obstructive symptoms [Chapple, *Brit. J. Urol.* 1: 47-55 (1995), Kawabe and Niijima, *Urol. Int.* 42: 280-284 (1987), Lepor et al, *J. Urol.* 148: 1467-1474 (1992), Reuther and Aagard, *Urol. Int.* 39: 312-313 (1984), Serels and Stein, *Neurourol. Urodyn.* 17: 31-36 (1998)]. In addition these α_1 AR antagonists have also been found to relieve the irritative bladder symptoms associated with BPH.

Alpha adrenoceptors are members of a larger G protein-coupled adrenergic receptors family, which mediates the actions of endogenous catecholamines norepinephrine and epinephrine resulting in smooth muscle contraction. cDNA's encoding

three distinct α_1 AR subtype (α_{1a} , α_{1b} and α_{1d}) and three distinct α_2 adrenoceptor subtypes (α_{2a} , α_{2b} and α_{2c}) have been cloned, expressed stably in cells and resultant protein characterized pharmacologically [Schwinn et al, *J. Pharmacol. Exper. Ther.* 272: 134-142 (1995), Hieble et al., *Pharmacol. Rev.* 47: 267-70 (1995)].

5 Human lower urinary tract contains both α_1 and α_2 AR, with the latter predominating the former [Goepel et al., *Urol. Res.* 25:199-206 (1997)]. However the prostatic smooth muscle contraction is mediated predominantly, if not exclusively by α_1 -AR [Hieble et al., *Eur. Pharmacol.* 107: 111-117(1985), Chappel et al., *Brit. J. Urol.* 63: 487-496 (1989)].

10 α_1 ARs predominate in prostate and bladder trigone [Price et al., *J. Urol.* 150: 546-551 (1993)], and have been shown to be functionally important in mediating smooth muscle contraction [Forray et al., *Mol. Pharmacol.* 45: 703-708 (1994), Lepor et al., *J. Pharmacol. Exper. Ther.* 270:722-727 (1994)]. In addition to the three-cloned α_1 AR subtypes which have high affinity for the prazosin a fourth type of α_1 AR with low affinity 15 for prazosin (α_{1L}) has been postulated [Muramatsu et al., *Brit. J. Urol.* 74: 572-578 (1994)]. However, there is evidence to suggest that it may represent functional phenotype of the α_1 AR [Daniels D.V., *Eur. J. Pharmacol.* 370: 337-43(1990)].

20 The non-subtype selective α_1 AR antagonists such as prazosin, terazosin and doxazosin and alfuzosin are accompanied by side effects such as postural hypotension, dizziness and syncope. These side effects are attributed to the affinity towards non-selective α_1 AR subtypes in the vasculature [*J. Androl.* 18: 345-355 (1991)]. Therefore, in an attempt to develop α_1 AR antagonist with minimal cardiovascular effect, the concept 25 of developing α_{1a} subtype selective antagonists with minimal affinity for α_{1b} and α_{1d} subtype in BPH was proposed which is extensively covered in United States Patent Nos. 5,403,847; 5,578,611; 5,780,485; 5,990,128; and 6,015,819.

30 Development of several α_{1a} subtype selective compounds with minimal affinity for α_{1b} and/or α_{1d} AR has been reported. The selective α_{1a} AR antagonists cause significantly smaller blood pressure alterations and fewer cases of orthostatic hypertension, as compared to nonselective α_1 AR antagonists [Michael M. C., *Eur. Urol. Supp.* 5-13 (2002)].

Recent studies, however suggest that the relief of bladder outlet obstruction only partly explain involvement of lower urinary tract with these agents. There is poor correlation in BPH patients between obstructive (voiding) and irritative (storage) symptoms and urine flow rates at base line. The irritative symptoms can persist despite the 5 relief of bladder outlet obstruction [Hieble and Ruffolo, Jr., *Exp. Opin. Invest. Drug* 6: 367-387 (1997)].

In recent clinical studies with experimental antagonists with high affinity for α_{1a} ARs and particularly devoid of α_{1d} activity have demonstrated enhancements in the urine flow rates without any improvement on irritative LUTS [Blue et al., *J. Urol.* 167 (Suppl) 10 265 (2002)].

Irritative symptoms such as urgency and frequency traditionally associated with BPH is also observed in LUTS in women suffering from detrusor instability suggesting thereby these symptoms are caused by similar mechanisms or are amenable to a single form of therapy [Staskin, D. R. et al., *Urology* 60 (Suppl 5A) (2002) 1-6].

15 The two main functions of the urinary bladder are to store urine and to empty it, by involving a complex pattern of nerve signalling. Disturbances in the normal control of the bladder reflexes may lead to an "overactive bladder", clinically characterized by symptoms of urgency, frequency, nocturia and urge incontinence. Bladder excitability is under the control of parasympathetic nervous system and releases the neurotransmitter 20 acetylcholine. Acetylcholine acts on protein recognition sites in bladder known as muscarinic receptors.

Muscarinic receptors are G-protein coupled receptors, encoded by five distinct genes [Caulfield and Birdsall, *Pharmacol. Rev.* 50: 279-290 (1998)]. These characterize five distinct molecular and pharmacological subtypes namely M1, M2, M3, M4 and M5. 25 Normal human bladder contraction is mediated mainly through stimulation of muscarinic receptors in detrusor muscle by the endogenous ligand, acetylcholine. The muscarinic receptors found in human detrusor are of M2 and M3 subtypes [Hedge and Eglen, *Life Sci.* 64: 419-428 (1999), Fetscher et al., *Brit. Jr. Pharmacol.* 136: 641-644 (2002)]. M2 receptors predominate in number over M3 subtype but it is M3 receptors, which are 30 mainly responsible for the normal micturition contraction [Yamanishi et al., *World J. Urol.* 19: 299-306 (2001)]. Muscarinic receptors are involved in both normal and disturbed bladder contraction, and therefore the most common drug treatment of

overactive bladder are muscarinic receptor antagonists also referred to as antimuscarinic drugs. Antimuscarinics block more or less selectively muscarinic receptors on the bladder smooth muscles (detrusor), which are stimulated by acetylcholine. Thereby they decrease the ability of bladder to contract. Antimuscarinic drugs act mainly during the storage phase, increase the bladder capacity and decrease the urge.

5 In the patients of outflow obstruction, as in BPH, muscarinic receptor antagonists have generally been contraindicated for symptomatic relief because of the possible risk of urinary retention [Sullivan et al., *Eur. Urol.* 36 (Suppl 1), 89-95 (1999)]. A number of reports of urinary outflow obstruction induced in patients given ipratropium by aerosol for 10 respiratory conditions have been recorded by Lozewicz [Lozewicz, S., *Postgrad Med. J.* 65: 260-261 (1989)]. These patients were found to have enlarged prostate gland.

Recently, administration of tolterodine, a antimuscarinic drug in men with bladder outlet obstruction and symptomatic detrusor overactivity was not associated with any safety concerns [Abrams, P. et al., *Eur. Urol.* 1: 132 (2002) (abstract 520)]. A combination therapy for the treatment of BPH comprising α_{1a} AR antagonist and an endothelin antagonist has been disclosed in U.S. Patent No. 6,410,554. A combination of a dyphylline-type compound with α AR antagonist and/or 5 α - reductase inhibitor for the treatment of BPH has been disclosed in U.S. Patent No. 6,423,719. WO 99/57131 discloses a method of identifying α_{1d} AR antagonists that can be used to treat irritative 15 symptoms of BPH. A combination of α_{1a} AR antagonist with 5 α -reductase inhibitor for the treatment of BPH has been disclosed in U.S. Patent No. 6,376,503. A method of treating LUTS and pharmaceutical composition comprising a muscarinic receptor antagonist and at least one other active ingredient selected from a 5 α -reductase inhibitor 20 and an α AR antagonist have been disclosed in WO 01/21167. Pharmaceutical combinations comprising α AR antagonist and a muscarinic receptor antagonist for the treatments of LUTS associated with BPH in men are disclosed in U.S. Patent Application 25 No. 2001/0044438.

Combinations of selective α_{1a} subtype adrenoceptor antagonists with muscarinic receptor antagonists are not previously known, therefore, patients are prone to side effects 30 (such as hypotension) associated with non-selective $\alpha 1$ AR antagonist.

Summary of the Invention

Herein is provided a combination of a selective α_{1a} AR antagonists, muscarinic receptor antagonists, and optionally included testosterone 5 α -reductase inhibitors for use as a medicament for the treatment of BPH and LUTS, whether or not associated with
5 BPH.

The pharmaceutical compositions provided herein can comprise a combined preparation of a first pharmaceutically acceptable composition comprising a selective α_{1a} AR antagonist, a second composition comprising a muscarinic receptor antagonist, and an optionally included third pharmaceutically acceptable composition comprising a 5 α -reductase inhibitor. The combined preparation may be used simultaneously, separately or
10 sequentially.

Further provided herein is a pharmaceutical composition comprising a selective α_{1a} AR antagonist, a muscarinic receptor antagonist and, optionally included, a testosterone 5 α -reductase inhibitor and a pharmaceutically acceptable carrier for the treatment of BPH
15 and LUTS, whether or not associated with BPH.

Methods for the treatment of BPH and LUTS in a mammal are also provided comprising administering to mammal in need thereof an effective amount of a selective α_{1a} AR antagonist in combination with a muscarinic receptor antagonist and optionally included testosterone 5 α -reductase inhibitor. The combination may be administered
20 simultaneously, separately or sequentially.

The combination of α_{1a} selective antagonist and muscarinic selective antagonists offers advantages of relieving LUTS more effectively in patients with BPH and obstructive symptoms, with minimal side effects such as fall in blood pressure. This combination will also be useful in obstructive LUTS in women and treatment of LUTS in
25 men in absence of BPH.

Detailed Description of the Invention

Along with the individual components of the composition, their pharmaceutically acceptable salts are also included. The pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of acids or bases. Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Example of such inorganic acids include, but are not limited to, hydrochloric,
30

hydrobromic, hydroiodic, nitrous (nitrite salt), nitric (nitrate salt), carbonic, sulfuric, phosphoric acid and like. Appropriate organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids such as, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, 5 malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, algenic, beta-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable 10 pharmaceutically acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, and procaine and the like. The salt forms can differ from the compounds described herein in 15 certain physical properties, such as solubility in polar solvent, but the salts generally retain the physiological utility of the non-salt compounds.

Prodrugs of these pharmaceutical agents are also provided herein. In general, such prodrugs will be functional derivatives of these compounds, which are readily convertible *in vivo* into the required compound. Conventional procedures for the selection 20 and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed.H Bundgaard et al. and, Elsevier, 1985. Metabolites, which become active upon introduction into the biological system, are also included herein. Where the compounds described herein have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds described herein possess two or more chiral centers, 25 they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures therefore are provided in this disclosure. Furthermore, some of the crystalline forms for compounds described herein may exist as polymorphs and as such are included in the present disclosure. In addition, some of the compounds described herein may form solvates with water (i.e., hydrates) or common organic solvents, and such 30 solvates are also provided herein.

The term "selective" as used in "selective α_{1a} AR antagonist" refers to those agents, which are more than about ten fold selective for α_{1a} AR as compared to α_{1b} and/or

α_{1d} ARs in receptor binding assay or *in vitro* functional assay. Particular selective α_{1a} AR antagonists can be, for example:

- 5,6-Dihydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]propyl}-hexahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,
- 5 -1-{3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl}-piperidine-2,6-dione and its pharmaceutically acceptable salts,
- 2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,
- 10 -1-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)piperidine-2,6-dione and its pharmaceutically acceptable salts,
- 5-Hydroxy-2-(3-{4-[2-(2,2,2-trifluoroethoxyphenyl]-piperazin-1-yl}propyl)-hexahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,
- 2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,
- 15 -2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-5,6-dihydroxy-isoindole-1,3-dione and its pharmaceutically acceptable salts,
- 4,7-Dihydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]propyl}-hexahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,
- 3-Allyl-1-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-4-methyl-pyrrolidine-2,5-dione and its pharmaceutically acceptable salts, and
- 20 -1-(2-Hydroxy-3-{4-[2-(2,2,3,3,3-pentafluoropropoxy)phenyl]-piperazin-1-yl}propyl)-piperidine-2,6-dione and its pharmaceutically acceptable salts.

The muscarinic receptor antagonists (MRAs) may be widely chosen from among those already known to the prior art or subsequently discovered and/or hereafter discovered and/or hereafter developed. MRAs have been described in United States Patent Nos. 5,096,890 and 5,233,053; EP 388054, EP 325571, EP 801067, GB 940540, and WO 98/05641. Particular MRSs can be, for example:

- (R)-2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-phenol (tolterodine) and its pharmaceutically acceptable salts,
- (S)-alpha-cyclohexyl-alpha-hydroxybenzaeneacetic acid-4-(diethylamino)-2-butynyl ester (oxybutynin) and its pharmaceutically acceptable salts,
- 5 -(S)-1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]alpha,alpha-diphenyl-3-pyrrolidine acetamide (darifenacin) and its pharmaceutically acceptable salts,
- (1S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl-3,4-dihydro-1-phenyl-2(1H)-isoquinolinecarboxylate (solifenacin) and its pharmaceutically acceptable salts,
- 10 -2-[(1R)-3-(diisopropylamine)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate and its pharmaceutically acceptable (fesoterodine),
- 2-Methyl- α,α -diphenyl-1H-imidazole and its pharmaceutically acceptable salts (KRP197),
- (2R)(+)(1 α , 5 α , 6 α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenylacetamide and its pharmaceutically acceptable salts,
- 15 -(2R, 2S) (1 α , 5 α , 6 α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenylacetamide and its pharmaceutically acceptable salts,
- (2R) (1 α , 5 α , 6 α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenylacetamide and its pharmaceutically acceptable salts,
- 20 -(2S) (1 α , 5 α , 6 α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenylacetamide and its pharmaceutically acceptable salts.

Testosterone 5 α -reductase inhibitors may be widely chosen from among those already known to the prior art or subsequently discovered and/or hereafter discovered and/or hereafter developed. The compounds that are inhibitor of testosterone 5 α -reductase inhibitor have been disclosed in United States Patent Nos. 5,595,985; 4,377,584; 25 4,760,071; 5,017,568; 5,155,107; and 5,565,467; EP 0572165, WO 93/23420, EP 0572166, WO 93/23050, WO 93/23038, WO 93/23048, WO 93/23041, WO 93/23040, WO 93/23039, WO93/23376, WO 93/23419, and WO 93/23051. Compounds may be

inhibitor of a type 1 or type 2 testosterone 5 α -reductase isoenzymes or both a type 1 and type 2 or a dual type 1 and type 2, preferably a dual type 1 and type 2 or a type 2 inhibitor, these compounds can be, for example, finasteride, dutasteride, epristeride or turosteride.

There are provided products or medicaments comprising a pharmaceutically acceptable composition containing a therapeutically effective amount of a selective α_{1a} AR antagonist disclosed herein and a second pharmaceutically acceptable composition containing therapeutically effective amount of a muscarinic receptor antagonist and optionally included therapeutically effective amount of testosterone 5 α -reductase inhibitor as a combined preparation for simultaneous, separate or sequential administration for the treatment of BPH and LUTS with or without BPH. LUTS may include, for example, obstructive symptoms such as hesitancy, poor stream, prolong urination, and feelings of incomplete emptying, and irritative symptoms such as frequency, urgency, nocturia and unstable bladder contractions. The term "therapeutically effective amount," as used herein, means that amount of active compound that elicits the biological or medicinal response in a mammal which provides at least partial alleviation of some symptoms of the disease being treated.

There are also provided pharmaceutical compositions containing a therapeutically effective amount of a selective α_{1a} AR antagonist disclosed herein, a therapeutically effective amount of a muscarinic receptor antagonist and optionally a therapeutically effective amount of testosterone 5 α -reductase inhibitor for the treatment of BPH and LUTS with or without BPH.

There are also provided pharmaceutical compositions containing selective alpha 1a AR antagonist as disclosed herein, a MR antagonist and optionally a testosterone 5-alpha reductase inhibitor in combination with pharmaceutically acceptable carriers, diluents or excipients.

The compositions described herein include both those containing only one component and those containing selective α_{1a} AR, muscarinic receptor antagonist and optionally included testosterone 5 α -reductase inhibitor, which may be suitable for oral, parenteral, topical, transdermal, chlonic or intravaginal administration. The composition may be formulated to provide immediate or sustained release of the therapeutic agents. The agents described herein can be administered alone but will generally be administered as an admixture with a suitable "pharmaceutically acceptable carrier". The term

"pharmaceutically acceptable carrier" is intended to include non-toxic, inert solid, semi-solid or liquid filter, diluent, encapsulating material or formulation auxiliary of any type.

Solid form preparations for oral administration may include capsules, tablets, pills, powders, granules and suppositories. For solid form preparations, an active compound is
5 mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate, dicalcium phosphate and/or a filter an extender such as starch, lactose, sucrose, glucose, mannitol and silicic acid; binders such as carboxymethyl cellulose, alginates, gelatins, polyvinylpyrrolidinone, sucrose, acacia; disintegrating agents such as agar-agar, calcium carbonate, potato starch, alginic acid, certain silicates and sodium
10 carbonate; absorption accelerators such as quaternary ammonium compounds; wetting agents such as cetyl alcohol, glycerol, monostearate; adsorbents such as kaolin; lubricants such as talc, calcium stearate, magnesium stearate, solid polyethyleneglycol, sodium lauryl sulphate and mixture thereof.

In case of capsules, tablets, or pills, the dosage form may also comprise buffering
15 agents. Solid preparations of tablets, capsules, pills, granules can be prepared with coating and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art.

Liquid form preparations for oral administration can include pharmaceutically acceptable emulsions, solution, suspensions, syrups and elixirs. For liquid form
20 preparations, an active compound is mixed with water or other solvent, solubilizing agents and emulsifiers such as ethylalcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (such as cottonseed, groundnut, corn, germ, olive, castor and sesame oil), glycerol and fatty acid ester of sorbitan and mixture thereof.

Besides inert diluents, oral compositions can also include adjuvants such as wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents and perfuming agent.

Injectable preparations such as sterile injections, aqueous or oleaginous suspensions may be formulated according to the art using suitable dispersing or wetting
30 and suspending agents. Among the acceptable vehicles and solvents that may be employed are water, Ringers solution and isotonic sodium chloride.

Dosage forms for topical or transdermal administration include ointments, pastes, creams, lotions, gel, powders, solutions, spray, inhalants or patches. The active compound

is admixed under sterile condition with a pharmaceutically acceptable carrier and any needed preservatives or buffer as may be required.

The pharmaceutical preparation can be prepared in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component.

The formulations as described herein may be formulated so as to provide quick sustained, or delayed release of the active ingredients after administration to the patient by employing procedures well known to the art. The compositions may be administered as a depot formulation that permits sustained release, limits access to general circulation, and increases the prostate and/or bladder-specific localization of the composition. Such a formulation may be provided as a slow release implant, be microencapsulated, or attached to a biodegradable polymers or a prostate-specific immunoglobulin. The compound is administered in a sustained release formulation as a tablet or capsule. A sustained release formulation is a preparation that releases the active component over a desired period of time after administration. A sustained release formulation is prepared by applying a biodegradable, bioerodible or bioabsorbable polymeric formulation that is compatible on the surface of the active component. Examples of sustained release formulations include, but are not limited to, hydroxypropylmethylcellulose (HPMC), hydrogenated vegetable oil (HVO), ethylcellulose, polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacryl – amidephenol, polyhydroxy – ethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydro-pyrans, or polycyano acrylates.

The term “biodegradable” means that the polymeric formulation degrades over time by the action of enzymes, by hydrolytic action and/or by other similar mechanisms in the human body. By “bioerodible” it is meant that the polymeric formulation erodes or degrades over time due, at least in part, to contact with substances found in the surrounding tissue fluids or cellular action. By “bioabsorbable”, it is meant that the polymeric formulation is broken down and absorbed within the body of a mammal, for example, by a cell or tissue. “Biocompatible” means that the polymeric formulation does not cause substantial tissue irritation or necrosis.

The compounds described herein can also be administered in the form of liposome delivery systems, for example, small unilamellar vesicles, large unilamellar vesicles and

multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, for example, cholesterol, stearylamine or phosphatidylcholines.

Aqueous parenteral compositions, may contain a therapeutically effective amount of selective alpha 1a AR antagonists disclosed herein, muscarinic receptor antagonist and 5 optionally included 5-alpha reductase inhibitor. The invention also provides a method of delivery such that direct intraprostatic injection of therapeutically effective amount of disclosed compositions result in the relieve of the obstructive symptoms associated with benign prostatic hyperplasia.

Methods of treating BPH and LUTS with or without BPH are also provided 10 comprising the administration of a therapeutically effective amount of selective α_{1a} AR antagonist, therapeutically effective amount of a muscarinic receptor antagonist and optionally included testosterone 5 α -reductase inhibitor to mammal in need thereof. The combined preparation can be administered simultaneously, separately or sequentially.

Methods for the treatment of BPH or LUT with or without BPH, comprising 15 administering a single dosage form containing a therapeutically effective amount of selective α_{1a} AR antagonist as disclosed herein, therapeutically effective amount of a MR antagonist and optionally included testosterone 5 α -reductase inhibitor to a mammal in need thereof.

The suitability of alpha 1a adrenergic receptor antagonists in this invention can be 20 determined using the assay methods, for example, those disclosed in *J. Auton. Pharmacol.* (1996), 16:21.

The suitability of muscarinic receptor antagonists in this invention can be determined using the assay methods, for example, those disclosed in *Life Sci.* (1999) 25 64:2351 and *J. Med. Chem.* (1999) 42:1999.

The pharmaceutical compositions as described herein can be administered together 30 combined in a single dosage form or they can be administered separately, simultaneously or sequentially, each in its dosage form but as part of the same therapeutic treatment program or regimen. Separate administration of each compound, at different times and by different routes, will sometimes be recommended.

Other pharmaceutical component may also optionally be included as part of the combination for the treatment of BPH and LUTS associated with or without BPH.

We claim:

- 1 1. A pharmaceutical product or medicament comprising a first component selected
2 from
 - 3 - 5,6-dihydroxy-2-{3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl}-hexahydro-
4 isoindole-1,3-dione,
 - 5 - 1-{3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl}-piperidine-2,6-dione,
 - 6 - 2-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-
7 dione,
 - 8 - 1-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)piperidine-2,6-dione,
 - 9 - 5-hydroxy-2-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-
10 hexahydro-isoindole-1,3-dione,
 - 11 - 2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-5-hydroxy-hexahydro-isoindole-
12 1,3-dione,
 - 13 - 2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-5,6-dihydroxy-isoindole-1,3-dione,
 - 14 - 4,7-dihydroxy-2-{3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl}-hexahydro-
15 isoindole-1,3-dione,
 - 16 - 3-Allyl-1-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-4-methyl-pyrrolidine-2,5-
17 dione,
 - 18 - 1-(2-Hydroxy-3-{4-[2-(2,2,3,3,3-pentafluoropropoxy)phenyl]-piperazin-1-
19 yl}propyl)-piperidine-2,6-dione
- 20 or their pharmaceutically acceptable salts,
- 21 a second component comprising a muscarinic receptor antagonist,
- 22 an optional third component comprising testosterone 5 α -reductase inhibitor and a
23 pharmaceutically acceptable carrier.
- 1 2. A product or medicament according to claim 1 wherein the product or medicament
2 is a combined preparation.
- 1 3. A product or medicament according to claim 2 wherein the combined preparation
2 is a single dosage form.

1 4. A product or medicament according to claim 2 wherein the combined preparation
2 comprise different dosage forms.

1 5. A product or medicament according to claim 1 wherein the muscarinic receptor
2 antagonist is selected from

3 - (R)-2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-phenol,
4 - (S)-alpha-cyclohexyl-alpha-hydroxybenzaeneacetic acid-4-(diethylamino)-2-butynyl
5 ester,
6 - (S)-1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]alpha,alpha-diphenyl-3-pyrrolidine
7 acetamide,
8 - (1S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl-3,4-dihydro-1-phenyl-2(1H)-
9 isoquinolinecarboxylate,
10 - 2-[(1R)-3-(diisopropylamine)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate,
11 - 2-Methyl- α,α -diphenyl-iH-imidazole,
12 - (2R)(+)(1 α , 5 α , 6 α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-
13 hydroxy-2-cyclopentyl-2-phenylacetamide,
14 - (2R, 2S) (1 α , 5 α , 6 α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-
15 2-cyclopentyl-2-phenylacetamide,
16 - (2R) (1 α , 5 α , 6 α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-
17 cyclopentyl-2-phenylacetamide,
18 - (2S) (1 α , 5 α , 6 α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-
19 cyclopentyl-2-phenylacetamide
20 or their pharmaceutically acceptable salts.

1 6. A product or medicament according to claim 1 wherein the testosterone 5 α -
2 reductase inhibitor is a type 1 or a type 2 or both a type 1 and type 2 or a dual type 1 and
3 type 2 inhibitor.

1 7. A product or medicament according to claim 6 wherein the testosterone 5 α -
2 reductase inhibitor is a dual type 1 and type 2 inhibitor.

1 8. A product or medicament according to claim 7 wherein the dual type 1 and type 2
2 inhibitor is dutasteride.

1 9. A product or medicament according to claim 6 wherein the testosterone 5 α -
2 reductase inhibitor is a type 2 inhibitor.

1 10. A product or medicament according to claim 9 wherein the type 2 inhibitor is
2 finasteride.

1 11. A method for treatment of a mammal suffering from benign prostatic hyperplasia
2 (BPH), lower urinary tract symptoms (LUTS) associated with or without BPH, comprising
3 administering to said mammal, a therapeutically effective amount of a product or
4 medicament, comprising

5 - 5,6-dihydroxy-2-{3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl}-hexahydro-
6 isoindole-1,3-dione,

7 - 1-{3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl}-piperidine-2,6-dione,

8 - 2-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-
9 dione,

10 - 1-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)piperidine-2,6-dione,
11 - 5-hydroxy-2-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-
12 hexahydro-isoindole-1,3-dione,

13 - 2-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl}-5-hydroxy-hexahydro-isoindole-1,3-
14 dione,

15 - 2-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl}-5,6-dihydroxy-isoindole-1,3-dione,
16 - 4,7-dihydroxy-2-{3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl}-hexahydro-
17 isoindole-1,3-dione,

18 - 3-allyl-1-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-4-methyl-pyrrolidine-2,5-
19 dione,

20 - 1-(2-Hydroxy-3-{4-[2-(2,2,3,3,3-pentafluoropropoxy)phenyl]-piperazin-1-
21 yl}propyl)-piperidine-2,6-dione

22 or their pharmaceutically acceptable salts, a muscarinic receptor antagonist and optionally
23 included testosterone 5 α -reductase inhibitor.

1 12. The method according to claims 11 wherein mammal is animal.

1 13. The method according to claims 11 wherein mammal is human.

- 1 14. The method according to claim 13 wherein human is man.
- 1 15. The method according to claim 13 wherein human is woman.
- 1 16. The method according to claims 11 wherein the said product or medicament is
2 administered as a combined preparation.
- 1 17. The method according to claim 16 wherein the combined preparation is
2 administered as single dosage forms.
- 1 18. The method according to claim 16 wherein the combined preparation is
2 administered in different dosage form.
- 1 19. The method according to claim 18 wherein the different dosage forms are
2 administered simultaneously.
- 1 20. The method according to claim 18 wherein the different dosage forms are
2 administered separately.
- 1 21. The method according to claim 18 wherein the different dosage forms are
2 administered sequentially.
- 1 22. The method according to claims 11 wherein muscarinic receptor antagonist is
2 selected from
 - 3 - (R)-2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-phenol (tolerodine),
 - 4 - (S)-alpha-cyclohexyl-alpha-hydroxybenzaeneacetic acid-4-(diethylamino)-2-butynyl
5 ester (oxybutynin),
 - 6 - (S)-1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]alpha,alpha-diphenyl-3-pyrrolidine
7 acetamide (darifenacin),
 - 8 - (1S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl-3,4-dihydro-1-phenyl-2(1H)-
9 isoquinolinecarboxylate (solifenacin),
 - 10 - 2-[(1R)-3-(diisopropylamine)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate,
 - 11 - 2-Methyl- α,α -diphenyl-iH-imidazole and its pharmaceutically acceptable salts,
 - 12 - (2R)(+)(1 α , 5 α , 6 α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-
13 hydroxy-2-cyclopentyl-2-phenylacetamide,
 - 14 - (2R, 2S) (1 α , 5 α , 6 α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-
15 2-cyclopentyl-2-phenylacetamide,

16 - (2R) (1 α , 5 α , 6 α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-
17 cyclopentyl-2-phenylacetamide,

18 - (2S) (1 α , 5 α , 6 α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-
19 cyclopentyl-2-phenylacetamide

20 and their pharmaceutically acceptable salts.

1 23. The method according to claim 11 wherein said testosterone 5 α -eductase inhibitor
2 is a type 1 or a type 2 or both a type 1 and type 2 or a dual type 1 and type 2 inhibitor.

1 24. The method according to claim 23 wherein the testosterone 5 α -reductase inhibitor
2 is a dual type 1 and type 2 inhibitor.

1 25. The method according to claim 24 wherein the dual type 1 and type 2 inhibitor is
2 dutasteride.

1 26. The method according to claim 23 wherein the testosterone 5 α -reductase inhibitor
2 is a type 2 inhibitor.

1 27. The method according to claim 26 wherein the type 2 inhibitor is finasteride.

1 28. A pharmaceutical product or medicament comprising a first pharmaceutical
2 composition of a component selected from

3 - 5,6-dihydroxy-2- {3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]propyl}-hexahydro-
4 isoindole-1,3-dione,

5 - 1-{3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl}-piperidine-2,6-dione,

6 - 2-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-
7 dione,

8 - 1-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)piperidine-2,6-dione,

9 - 5-hydroxy-2-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-
10 hexahydro-isoindole-1,3-dione,

11 - 2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-5-hydroxy-hexahydro-isoindole-
12 1,3-dione,

13 - 2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-5,6-dihydroxy-isoindole-1,3-dione,
14 - 4,7-dihydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]propyl}-hexahydro-
15 isoindole-1,3-dione,

- 16 - 3-Allyl-1-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-4-methyl-pyrrolidine-2,5-
17 dione,
18 - 1-(2-Hydroxy-3-{4-[2-(2,2,3,3,3-pentafluoropropoxy)phenyl]-piperazin-1-
19 yl}propyl)-piperidine-2,6-dione
20 or their pharmaceutically acceptable salts,
21 a second pharmaceutical composition of a muscarinic receptor antagonist,
22 an optional third pharmaceutical composition of testosterone 5 α -reductase inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/000842

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/496 A61K31/216 A61P13/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 123 705 A (PFIZER PRODUCTS INC) 16 August 2001 (2001-08-16) the whole document -----	1-28
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		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *V* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

28 February 2005

Date of mailing of the international search report

10/03/2005

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/000842

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2004/014853 A (RANBAXY LABORATORIES LIMITED; MEHTA, ANITA; SILAMKOTI, ARUNDUTT, V; KA) 19 February 2004 (2004-02-19) the whole document -----	1-28
A	WO 2004/018422 A (RANBAXY LABORATORIES LIMITED; MEHTA, ANITA; GUPTA, JANG BAHADUR) 4 March 2004 (2004-03-04) the whole document -----	1-28
A	KENNY B ET AL: "Pharmacological Options in the Treatment of Benign Prostatic Hyperplasia" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, no. 9, 25 April 1997 (1997-04-25), pages 1293-1315, XP002103453 ISSN: 0022-2623 the whole document -----	1-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/000842

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11–27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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